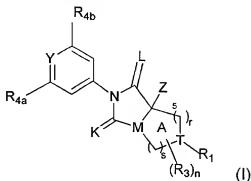


**CLAIMS**

We claim:

1. A compound having the formula (I),



- 5 or a pharmaceutically-acceptable salt thereof, in which:

L and K, taken independently, are O or S;

M is N or CH;

Y is CH or N;

- 10 Z is hydrogen, alkyl, or substituted alkyl, provided that Z may be selected from arylalkyl and heteroarylalkyl only when M is CH and/or when A has a second ring fused thereto;

T is nitrogen, CH, or a carbon atom substituted with an R<sub>3</sub> group;

- R<sub>1</sub> is Q-aryl or Q-heteroaryl, wherein (a) when T is not nitrogen, Q is selected from a bond, -O-, -NR<sub>10</sub>-, -S-, -C(=O)-, -CO<sub>2</sub>-, -OC(=O)-, -NR<sub>10</sub>C(=O)-, -C(=O)NR<sub>10</sub>-, -NR<sub>10</sub>CO<sub>2</sub>-, C<sub>1-4</sub>alkylene, C<sub>1-4</sub>substituted alkylene, C<sub>1-4</sub>alkenylene, C<sub>1-4</sub>substituted alkenylene, and optionally-substituted bivalent C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>aminoalkyl, C<sub>0-4</sub>alkylsulfonyl, C<sub>0-4</sub>alkylsulfonamide, C<sub>1-4</sub>acyl, or C<sub>1-4</sub>alkoxycarbonyl, or when Z is arylalkyl or heteroarylalkyl, R<sub>1</sub> may join with an R<sub>3</sub> group to form a fused carbocyclic or heterocyclic ring; or (b) when T is nitrogen, then Q is selected from a bond, -C(=O)-, -CO<sub>2</sub>-, -OC(=O)-, -C<sub>1-4</sub>alkylene, C<sub>1-4</sub>substituted alkylene, C<sub>1-4</sub>alkenylene, C<sub>1-4</sub>substituted alkenylene, or optionally-substituted bivalent C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, C<sub>1-4</sub>aminoalkyl, C<sub>0-4</sub>alkylsulfonyl, C<sub>0-4</sub>alkylsulfonamide,

C<sub>1-4</sub>acyl, or C<sub>0-4</sub>alkoxycarbonyl, provided that when M is N, T is N, *r* is 1, and *s* is 2 such that ring A is piperazine, R<sub>1</sub> is not an amine-protecting group;

R<sub>3</sub> is selected from (i) a substituent R<sub>3</sub>, wherein each substituent R<sub>3</sub> is individually attached to any available carbon or nitrogen atom of ring A and at each occurrence is selected independently of each other R<sub>3</sub> from halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, OR<sub>8</sub>, NR<sub>8</sub>R<sub>9</sub>, CO<sub>2</sub>R<sub>8</sub>, (C=O)R<sub>8</sub>, C(=O)NR<sub>8</sub>R<sub>9</sub>, NR<sub>8</sub>C(=O)R<sub>9</sub>, NR<sub>8</sub>C(=O)OR<sub>9</sub>, OC(=O)R<sub>8</sub>, OC(=O)NR<sub>8</sub>R<sub>9</sub>, SR<sub>8</sub>, S(O)<sub>q</sub>R<sub>8a</sub>, NR<sub>8</sub>SO<sub>2</sub>R<sub>9</sub>, SO<sub>2</sub>NR<sub>8</sub>R<sub>9</sub>, aryl, heteroaryl, heterocyclo, and cycloalkyl, and when attached to an atom of ring A other than T, R<sub>3</sub> is optionally keto (=O), provided that when R<sub>3</sub> is attached to the atom designated as the C-5 atom of ring A, then R<sub>3</sub> is not aryl or heteroaryl, and (ii) a first group R<sub>3</sub> and a second group R<sub>3</sub>, wherein the first group R<sub>3</sub> and the second group R<sub>3</sub> are attached to two adjacent atoms of ring A and together form an optionally-substituted carbocyclic or heterocyclic ring fused to ring A;

R<sub>4a</sub> and R<sub>4b</sub> are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, hydroxy, alkoxy, substituted alkoxy, phenyloxy, benzyloxy, CO<sub>2</sub>H, C(=O)H, amino, alkylamino, substituted alkylamino, CO<sub>2</sub>alkyl, (C=O)alkyl, and alkylthio;

R<sub>8</sub> and R<sub>9</sub> (i) selected independently of each other are hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heteroaryl, or heterocyclo; or (ii) taken together form a heterocyclo ring;

R<sub>8a</sub> is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo;

R<sub>10</sub> is hydrogen, alkyl, or substituted alkyl;

*n* is 0, 1, or 2;

*q* is 1, 2, or 3;

*r* is 1 or 2; and

s is 0, 1, or 2.

2. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, wherein:

5 at least one of L and K is O;

Y is CH;

Z is hydrogen, lower alkyl, or lower alkyl substituted with hydroxy, alkoxy, halogen, cyano, nitro, amino, or alkylamino;

10 T is nitrogen, CH, or CR<sub>3a</sub> wherein R<sub>3a</sub> is hydroxy, amino, alkylamino, halogen, cyano, or C<sub>1-4</sub> alkyl optionally substituted with hydroxy, amino, alkylamino, halogen, or cyano;

15 R<sub>1</sub> is Q-aryl or Q-heteroaryl, wherein (a) when T is not nitrogen, Q is selected from a bond -O-, -NR<sub>10</sub>-, -S-, -C(=O)-, -CO<sub>2</sub>-, -OC(=O), C<sub>1-4</sub>alkylene, C<sub>1-4</sub>substituted alkylene, C<sub>1-4</sub>alkenylene, C<sub>1-4</sub>substituted alkenylene, or optionally-substituted bivalent C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>aminoalkyl, C<sub>0-4</sub>alkylsulfonyl, C<sub>0-4</sub>alkylsulfonamide, C<sub>1-4</sub>acyl, and C<sub>0-4</sub>alkoxycarbonyl; or (b) when T is nitrogen, then Q is selected from a bond, -C(=O)-, -CO<sub>2</sub>-, -OC(=O), -C<sub>1-4</sub>alkylene, C<sub>1-4</sub>substituted alkylene, C<sub>1-4</sub>alkenylene, and C<sub>1-4</sub>substituted alkenylene;

20 R<sub>3</sub> is attached to any available carbon atom of ring A other than T and is selected from halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, OR<sub>8</sub>, NR<sub>8</sub>R<sub>9</sub>, CO<sub>2</sub>R<sub>8</sub>, (C=O)R<sub>8</sub>, C(=O)NR<sub>8</sub>R<sub>9</sub>, NR<sub>8</sub>C(=O)R<sub>9</sub>, NR<sub>8</sub>C(=O)OR<sub>9</sub>, OC(=O)R<sub>8</sub>, OC(=O)NR<sub>8</sub>R<sub>9</sub>, SR<sub>8</sub>, S(O)<sub>q</sub>R<sub>8a</sub>, NR<sub>8</sub>SO<sub>2</sub>R<sub>9</sub>, SO<sub>2</sub>NR<sub>8</sub>R<sub>9</sub>, aryl, heteroaryl, heterocyclo, cycloalkyl, and keto (=O), provided  
25 that when R<sub>3</sub> is attached to the atom designated as the C-5 atom of ring A, then R<sub>3</sub> is not aryl or heteroaryl;

$R_{4a}$  and  $R_{4b}$  are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, alkoxy, cyano, nitro, haloalkyl, and haloalkoxy;

$R_8$  and  $R_9$  selected independently of each other are hydrogen or alkyl, and  $R_{8a}$  is alkyl;

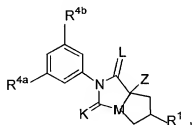
$R_{10}$  is hydrogen, lower alkyl, or lower alkyl substituted with  $CO_2H$  or  $CO_2alkyl$ ;

$n$  is 0 or 1;

$r$  is 1; and

$s$  is 1 or 2.

3. A compound according to claim 1 having the formula:

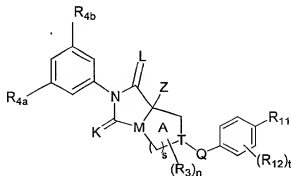


or a pharmaceutically-acceptable salt thereof.

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4. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which  $R_1$  is  $-O-C_{0-2}alkylene-phenyl$ ,  $-S-C_{0-2}alkylene-phenyl$ ,  $-NR_{10}-C_{0-2}alkylene-phenyl$ ,  $-C_{1-3}acyl-phenyl$ ,  $-C_{0-2}alkoxycarbonyl-phenyl$ , or  $-NR_{10}-SO_2-phenyl$ , and said  $R_1$  phenyl group has zero to two substituents selected from halogen,  $C_{1-4}alkyl$ , nitro, cyano, hydroxy,  $C_{1-4}alkoxy$ , haloalkyl, haloalkoxy,  $CO_2H$ ,  $C(=O)H$ , amino,  $C_{1-4}alkylamino$ ,  $CO_2C_{1-4}alkyl$ ,  $(C=O)C_{1-4}alkyl$ ,  $C_{1-4}alkylthio$ , phenyl, phenyloxy, benzyl, or benzyloxy.

5. A compound according to claim 1, having the formula,



or a pharmaceutically-acceptable salt thereof, wherein:

- 5        Z is hydrogen, alkyl, or alkyl substituted with hydroxy, alkoxy, halogen, cyano, nitro, amino, or alkylamino;

         R<sub>11</sub> is hydrogen, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, nitro, or cyano;

- R<sub>3</sub> and R<sub>12</sub> are independently selected from alkyl, substituted alkyl,  
10        halogen, haloalkyl, haloalkoxy, nitro, cyano, hydroxy, alkoxy, amino, alkylamino, acyl, alkoxy carbonyl, carbamyl, sulfonyl, and sulfonamide;

         n is 0 or 1;

         s is 1 or 2; and

         t is 0, 1, or 2.

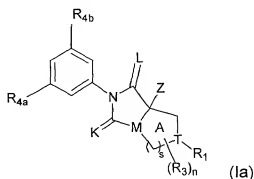
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6. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, in which R<sub>4a</sub> and R<sub>4b</sub> are both halogen.

7. The compound of claim 1, or a pharmaceutically-acceptable salt  
20        thereof, in which M is CH.

8. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, wherein M is N, T is N,  $r$  is 1 and  $s$  is 2 such that ring A is piperazine, and  $R_1$  is Q-aryl or Q-heteroaryl wherein Q is selected from a bond,  $-C(=O)-$ ,  $-CO_2-$ ,  $-OC(=O)-$ ,  $-C_{1-4}$ alkylene,  $C_{1-4}$ substituted alkylene,  $C_{1-4}$ alkenylene, and  $C_{1-4}$ substituted alkenylene, provided that Q- $R_1$  is not benzyl or carbobenzyloxy.

9. A compound having the formula (Ia),



- 10 or a pharmaceutically-acceptable salt thereof, in which:

L and K are O or S;

M is N or CH;

- Z is hydrogen, alkyl, alkyl substituted with hydroxy, halogen, cyano, amino, or alkylamino; or when  $R_1$  together with an  $R_3$  group join to form a benzo ring fused to ring A, Z is arylalkyl or heteroarylalkyl;

T is nitrogen or  $CR_5$ ;

$R_1$  is (a)  $-W-(CH_2)_m-Ar$ , or (b) taken together with an  $R_3$  group to form a benzo ring fused to ring A, in which case Z is arylalkyl or heteroarylalkyl;

- Ar is aryl or heteroaryl substituted with zero or one  $R_{11}$  and zero to two  $R_{12}$  groups;

W is selected from (a) when T is  $CR_5$ , a bond,  $-O-$ ,  $-NR_{10}-$ ,  $-S-$ ,  $-C(=O)-$ ,  $-CO_2-$ , and  $-CH(R_{13})-C(=O)-$ ; and (b) when T is nitrogen, a bond,  $-C(=O)-$ ,  $-$

CO<sub>2</sub>-, and -CH(R<sub>13</sub>)-C(=O)-, provided that when M is N, T is N, and s is 2 such that ring A is piperazine, then W-(CH<sub>2</sub>)<sub>m</sub>-Ar is not benzyl or carbobenzyloxy;

R<sub>3</sub> is selected from (i) a substituent R<sub>3</sub>, wherein each substituent R<sub>3</sub> is individually attached to any available carbon or nitrogen atom of ring A and at each occurrence is selected independently of each other R<sub>3</sub> from halogen, alkyl, substituted alkyl, alkenyl, nitro, cyano, keto (=O), OR<sub>8</sub>, NR<sub>8</sub>R<sub>9</sub>, CO<sub>2</sub>R<sub>8</sub>, (C=O)R<sub>8</sub>, C(=O)NR<sub>8</sub>R<sub>9</sub>, NR<sub>8</sub>C(=O)R<sub>9</sub>, NR<sub>8</sub>C(=O)OR<sub>9</sub>, OC(=O)R<sub>8</sub>, OC(=O)NR<sub>8</sub>R<sub>9</sub>, SR<sub>8</sub>, S(O)<sub>q</sub>R<sub>8a</sub>, NR<sub>8</sub>SO<sub>2</sub>R<sub>9</sub>, SO<sub>2</sub>NR<sub>8</sub>R<sub>9</sub>, aryl, heteroaryl, heterocyclo, and cycloalkyl; and (ii) a first group R<sub>3</sub> and a second group R<sub>3</sub>, wherein the first group R<sub>3</sub> and the second group R<sub>3</sub> are attached to two adjacent atoms of ring A and together form an optionally-substituted carbocyclic or heterocyclic ring fused to ring A, or one R<sub>3</sub> together with R<sub>1</sub> may join to form a fused benzo ring;

R<sub>5</sub> is hydrogen, halogen, alkyl, alkenyl, hydroxy, nitro, cyano, hydroxy, alkoxy, amino, or alkylamino, or C<sub>1-4</sub> alkyl optionally substituted with hydroxy, amino, alkylamino, halogen, or cyano;

R<sub>4a</sub> and R<sub>4b</sub> are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, nitro, cyano, haloalkyl, and haloalkoxy;

R<sub>8</sub> and R<sub>9</sub> (i) selected independently of each other are hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo; or (ii) taken together form a heterocyclo ring;

R<sub>8a</sub> is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo;

R<sub>11</sub> is hydrogen, halogen, alkyl, hydroxy, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, nitro, or cyano;

R<sub>12</sub> is alkyl, substituted alkyl, halogen, haloalkyl, haloalkoxy, nitro, cyano, hydroxy, alkoxy, substituted alkoxy, amino, alkylamino, acyl, alkoxycarbonyl, carbamyl, sulfonyl, or sulfonamide;

R<sub>10</sub> and R<sub>13</sub> are independently hydrogen, alkyl, or substituted alkyl;

$m$  is 0, 1, 2, 3, or 4;

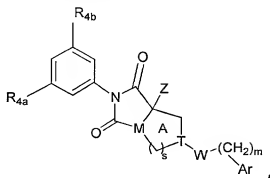
$n$  is 0, 1 or 2;

$q$  is 1, 2, or 3; and

$s$  is 1 or 2.

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10. A compound according to claim 9, having the formula:

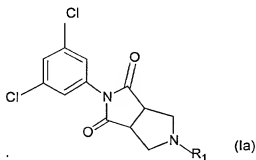


or a pharmaceutically-acceptable salt thereof.

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11. A compound according to claim 10, in which Ar is optionally substituted phenyl or isoquinolinyl and  $R_{4a}$  and  $R_{4b}$  are both halogen.

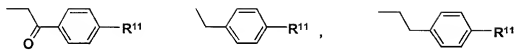
12. A compound according to claim 9 having the formula (Ia),



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in which

$R_1$  is selected from

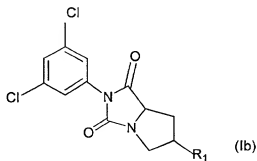


and

R<sub>11</sub> is selected from hydrogen, bromo, chloro, cyano, and methoxy.

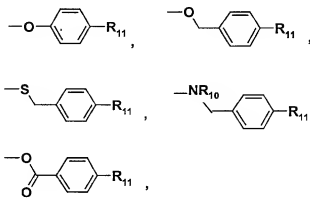
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13. A compound according to claim 9 having the formula (Ib),



in which R<sub>1</sub> is selected from:

10



R<sub>11</sub> is selected from hydrogen, bromo, chloro, cyano, and methoxy, and  
R<sub>10</sub> is selected from hydrogen and alkyl.

15

14. A compound according to claim 9 which is: (I)  
 (7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromophenoxy)-tetrahydro-  
 pyrrolo[1,2-c]imidazole-1,3-dione;  
 (7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromophenoxy)-tetrahydro-  
 5 pyrrolo[1,2-c]imidazole-1,3-dione;  
 5-[2-(4-Chlorophenyl)ethyl]-2-(3,5-dichlorophenyl)-tetrahydropyrrolo[3,4-  
 c]pyrrole-1,3-dione;  
 7-[2-(4-Bromophenyl)ethyl]-2-(3,5-dichlorophenyl)-tetrahydro-imidazo[1,5-  
 a]pyrazine-1,3-dione;  
 10 7-[2-(4-Bromophenyl)-1-methyl-2-oxo-ethyl]-2-(3,5-dichlorophenyl)-tetrahydro-  
 imidazo[1,5-a]pyrazine-1,3-dione;  
 (7aS,6S)-4-[[2-(3,5-dichloro-phenyl)-1,3-dioxo-hexahydro-pyrrolo[1,2-  
 c]imidazol-6-ylamino]-methyl]-benzonitrile;  
 (7aS,6S)-N-(4-cyano-benzyl)-N-[2-(3,5-dichloro-phenyl)-1,3-dioxo-hexahydro-  
 15 pyrrolo[1,2-c]imidazol-6-yl]-acetamide;  
 (6R,7aS)-[6-(4-bromobenzyloxy)-2-(3,5-dichlorophenyl)-1,3-dioxo-tetrahydro-  
 pyrrolo[1,2-c]imidazol-7a-yl]-acetic acid methyl ester;  
 5-[2-(4-Bromophenyl)-2-oxoethyl]-2-(3,5-dichlorophenyl)-  
 tetrahydropyrrolo[3,4-c]pyrrole-1,3-dione;  
 20 2-(3,5-Dichlorophenyl)-5-naphthalen-2-ylmethyl-tetrahydropyrrolo[3,4-  
 c]pyrrole-1,3-dione;  
 (7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromobenzyloxy)-tetrahydro-  
 pyrrolo[1,2-c]imidazole-1,3-dione;  
 10a-(4-Bromo-benzyl)-2-(3,5-dichloro-phenyl)-10,10a-dihydro-5H-  
 25 imidazo[1,5-b]isoquinoline-1,3-dione;  
 (6S,7aS)-6-(4-bromobenzyloxy)-2-(3,5-dichlorophenyl)-tetrahydro-  
 pyrrolo[1,2-c]imidazole-1,3-dione; or (ii) a pharmaceutically-acceptable salt  
 thereof.

15. A pharmaceutical composition for treating an inflammatory or immune disease comprising (a) at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

16. A pharmaceutical composition for treating an inflammatory or immune disease comprising (a) at least one compound according to claim 9, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

17. A pharmaceutical composition comprising (i) at least one compound of claim 1 or a pharmaceutically acceptable salt thereof; (ii) one or more second compositions effective for treating an inflammatory or immune disease; and (iii) a pharmaceutically-acceptable carrier.

18. A method of treating an inflammatory or immune disease comprising administering to a mammal in need of such treatment a therapeutically-effective amount of a composition according to claim 15.

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19. A method of inhibiting a Leukointegrin/ICAM-associated condition which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

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